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EXAMINER

ROARK, JESSICA H

ART UNIT	PAPER NUMBER
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1644

DATE MAILED: 07/07/2003

13

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/837,446

Applicant(s)

BUTCHER ET AL.

Examiner

Jessica H. Roark

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 21 January 2003 and 08 April 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 23-38 is/are pending in the application.
- 4a) Of the above claim(s) 33,34 and 36-38 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 23-32 and 35 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 17 April 2001 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 10.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

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DETAILED ACTION

1. Claims 23-38 are pending.

2. Applicant's election with traverse of the species of atopic dermatitis in Paper No. 9 is acknowledged. The traversal is on the grounds that the species overlap and one patient may have more than one disease. This is not found persuasive because although some overlap may sometimes be present, the patient populations are nevertheless recognized as distinct and a search for one condition is not co-extensive with a search for any others.

Applicant's election with traverse of Group I, drawn to a method wherein the CCR4 antagonist is an anti-CCR4 antibody in Paper No. 12 is also acknowledged. The traversal is on the grounds that a search of the entire application can be made without undue burden. This is not found persuasive because, as set forth in Paper No. 11 the methods require structurally distinct antagonists which require different fields of search.

The requirement is still deemed proper and is therefore made FINAL.

Claims 33-34 and 36-38 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected Group or species, there being no allowable generic or linking claim.

Claims 23-32 and 35 are under consideration in the instant application.

Drawings

3. The drawings submitted 4/17/01 have been approved by the Draftsman.

IDS

4. Applicant's IDS, filed 4/17/01 (Paper No. 10) is acknowledged.

Priority

5. The status of nonprovisional parent application 09/232,878 should also be included in the Cross Reference to Related Applications. The expression "now Patent No. 6,245,332" should be inserted following the filing date of the parent application.

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Specification

6. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which Applicant may become aware in the specification.

7. The Abstract is objected to because it appears to exceed 150 words in length. Applicant is requested to review the length of the Abstract to ensure that it is fewer than 150 words in length and revise the Abstract if needed.

8. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required:

The claims recite a method of inhibiting trafficking of memory T cells to a site of inflammation, wherein the site of inflammation is a site of atopic dermatitis, by administering a CCR4 antagonist.

However, the only disclosure of methods with respect to a site of inflammation that is a site of atopic dermatitis that the Examiner could identify in the specification as filed was with reference to administration of an agonist, rather than antagonist, of CCR4 (page 8 at lines 15-22).

It appears that the disclosure of an "agonist" on page 8 at lines 20-22 may have been in error.

An amendment to correct an obvious error does not constitute new matter where one skilled in the art would not only recognize the existence of error in the specification, but also the appropriate correction. In re Oda, 443 F.2d 1200, 170 USPQ 268 (CCPA 1971).

However, it is incumbent upon Applicant to provide along with any amendment to the specification to change the "agonist" disclosed on page 8 at line 21 to "antagonist" *sufficient support to show that both the error and the correction were obvious*.

Alternatively, Applicant is invited to point out antecedent basis elsewhere in the specification for the instantly recited subject matter.

Claim Rejections - 35 USC § 112 first paragraph

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

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10. Claim 35 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The specification as originally filed does not provide support for the invention as now claimed. *This is a New Matter rejection for the following reasons:*

Applicant's amendment filed 9/19/02 asserts that no New Matter has been added and points to the specification at page 24 line 9 to page 25 line 23, page 6 lines 16-22, pages 7 lines 9-11, page 11 lines 16-20, page 15 lines 15-17, Figures 1, 3, 5, 7, 8 and 9 and the original claims for support for the newly added claims.

However, the specification does not appear to provide an adequate written description of a method of inhibiting the trafficking of memory T cells to a site of inflammation by administering a CCR4 *antagonist*, wherein the site of inflammation is a site of atopic dermatitis.

The locations in the specification pointed to by Applicant do not appear to support the instantly recited combination of limitations. In addition, the Examiner was unable to identify support elsewhere in the specification for the above noted claim language. As noted supra, it is acknowledge that page 8 of the specification at lines 15-22 does disclose methods with respect to atopic dermatitis; however, page 8 at lines 20-22 disclose that it is an *agonist*, not an antagonist, that is administered.

The instant claims now recite limitations which were not clearly disclosed in the specification and claims as filed, and now change the scope of the instant disclosure as filed. Such limitations recited in the present claims, which did not appear in the specification or original claims, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

Applicant is invited to clearly point out the written support for the instant limitations or, as noted supra, show that the disclosure of "agonists" in the specification on page 8 at lines 20-22 was an obvious error for which the correction was also obvious.

11. Claims 23-31 and 35 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The following *written description* rejection is set forth herein.

Applicant's election of the a "CCR4 antagonist" that is an antibody to CCR4 in Paper No. 12 is acknowledged; however, the following rejection is set forth with respect to the breadth of the instant claim language.

The claims recite a method comprising administering "a CCR4 antagonist" as part of the invention.

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However, there does not appear to be an adequate written description in the specification as-filed of the essential structural feature that provides the recited function of antagonizing CCR4. The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. (See Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, especially page 1106 3rd column). A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. MPEP 2163 II.A.3a.ii.

Applicant discloses on page 11 of the specification at line 16 to page 17 at line 19 that a "CCR4 antagonist" may be a peptide, small organic molecule, peptidomimetic, soluble T cell receptor, antibody or the like, that a "CCR4 antagonist" may be from any of numerous chemical classes, and that a "CCR4 antagonist" may be either synthetic or natural.

The breadth of structures encompassed by the term "CCR4 antagonist" is very large, and there is substantial variation among the members. However, Applicant appears only to disclose a specific example of a "CCR4 antagonist": an antibody to CCR4 (e.g., specification pages 12-14). A single structure (an antibody) does not appear to provide a description of a sufficient variety of species to provide an adequate written description of the claimed genus. It does not appear based upon the limited disclosure that Applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the limited number of species disclosed and the extensive variation permitted within the genus of "CCR4 antagonists".

In addition, the specification on page 9 at lines 13-15 discloses that a "CCR4 antagonist" is any agent that blocks CCR4 biological activity, for example the interaction between CCR4 and its ligands (i.e., TARC and MDC). However, biological activity of CCR4 may be blocked by a number of mechanisms, including those that inhibit migration of CLA-expressing cells also expressing CCR4, without directly targeting the interaction of CCR4 and its ligands.

For example, Reiss et al. (J. Exp. Med. 2001;194(10):1531-1547) teach that an antibody to the chemokine CTACK also functions to abrogate skin recruitment of CLA-expressing memory T cells (see e.g., Abstract and Discussion). Similarly, Biedermann et al. (Eur. J. Immunol. 2002; 32 :3171-3180) teach that an anti-E-selectin antibody or a sialyl Lewis^x analog each prevent migration of Th2 memory T cells into human skin. Migration of CLA-expressing memory T cells into skin is a biological function of CCR4, as disclosed in the specification on, for example, page 7 at lines 21-28.

Thus the recitation of a "CCR4 antagonist" encompasses within the breadth of the instant claims a extensive genus of other compounds that also function as a "CCR4 antagonist" yet have widely differing structures and direct functions. However, Applicant does not appear to have provided an adequate written description of these compounds, either with respect to other possible non-antibody compounds that may inhibit the binding of CCR4 to its ligands TARC or MDC, or in particular with respect to other possible compounds, such as anti-E-selectin antibodies or sialyl Lewis^x analogs, that also antagonize CCR4 biological activity.

In the absence of an adequate written description of the "CCR4 antagonists" utilized in the instantly recited method; there does not appear to be an adequate written description of the method claimed.

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Consequently, Applicant was not in possession of the instant claimed invention. See Regents of the University of California v. Eli Lilly and Co. 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). Adequate written description of genetic material “requires a precise definition, such as by structure, formula, chemical name, or physical properties,” not a mere wish or plan for obtaining the claimed chemical invention.” Id. 43 USPQ2d at 1404 (quoting Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606). The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter of the claim. Id. 43 USPQ2d at 1406. A description of what the genetic material does, rather than of what it is, does not suffice. Id.

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 “Written Description” Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Alternatively, Applicant is invited to point to clear support or specific examples of the claimed invention in the specification as-filed.

12. Claims 23-31 and 35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting trafficking of systemic memory T cells to a site of inflammation that is a site of atopic dermatitis by administering an antibody to CCR4, does not reasonably provide enablement for method of inhibiting trafficking of systemic memory T cells to a site of inflammation that is a site of atopic dermatitis by administering a “CCR4 antagonist” in general. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Applicant’s election of the a “CCR4 antagonist” that is an antibody to CCR4 in Paper No. 12 is acknowledged; however, the following rejection is set forth with respect to the breadth of the instant claim language.

It would require undue experimentation to produce representative number of “CCR4 antagonists” for use in the instant method without more explicit guidance from the instant disclosure. While the specification discloses that “CCR4 antagonists” may possibly be identified by screening (e.g., pages 10-12), there appears to be insufficient guidance in the specification as filed to allow one skilled in the art to conduct such screening without extensive and undue experimentation.

Applicant discloses on page 11 of the specification at line 16 to page 17 at line 19 that a “CCR4 antagonist” may be a peptide, small organic molecule, peptidomimetic, soluble T cell receptor, antibody or the like, that a “CCR4 antagonist” may be from any of numerous chemical classes, and that a “CCR4 antagonist” may be either synthetic or natural.

The breadth of structures encompassed by the term “CCR4 antagonist” is very large; thus the scope of the instant claims is extensive. However, Applicant appears only to disclose a single specific example of a “CCR4 antagonist”, an antibody to CCR4 (e.g., specification pages 12-14), for which sufficient guidance has been provided such that the skilled artisan could produce this particular CCR4 antagonist without undue experimentation.

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Regarding other structures that might include a "CCR4 antagonist", it is noted that while some small molecule inhibitors of other chemokine receptors have been produced, the state of the art at the time the invention was made did not appear to recognize any small molecule inhibitors of the chemokine receptor CCR4 (e.g., see the Review by Schwarz et al., Cur. Opin. Chem. Biol. 1999; 3:407-417).

Further, the skilled artisan was well aware that successful design of inhibitors for any other chemokine receptor did not reduce the quantity of experimentation necessary, or assure the successful outcome, with respect to the design of small molecule inhibitors of any other particular chemokine receptor because in general the design/identification of small molecule inhibitors was highly unpredictable, especially in the absence of a lead compound. For example, Huang (Pharmacol. Therapeutics 2000 86:201-215) reviewed in his "Introduction" on page 202 the daunting task faced by the skilled artisan in developing small molecule regulators of protein-protein interactions, and noted that the process required long periods of trial and error testing before suitable compounds could be developed. Thus the structure of such molecules can not be readily envisioned by one skilled in the art based upon the guidance provided in the specification.

Even when small molecule inhibitors of chemokine:chemokine receptor interactions *in vitro* have been identified, the ability of a small molecule inhibitor to function *in vivo* can not be presumed until extensive *in vivo* testing and validation has been performed. Schwarz et al. (Cur. Opin. Chem. Biol. 1999; 3:407-417) note that even after the time the instant invention was made there was still a great deal of uncertainty as to whether those small molecule inhibitors that had thus far been identified (which did not appear to include inhibitors of CCR4) would actually function *in vivo* enough to impact disease (see e.g., concluding remarks on page 415). Gerard et al. (Nature Immunol. 2001; 2:108-115) echo this sentiment by noting that, even though there is clearly a role for individual chemokines and chemokine receptors in various disease states, "[t]he challenge now is to develop small molecule antagonists with good bioavailability, that is, drugs." (see e.g. page 114).

Therefore there is even greater uncertainty that any small molecule "CCR4 antagonist", even if one could be developed, could be used for inhibiting the trafficking of systemic memory T cells to a site of inflammation.

Applicant is reminded that "[i]t is not sufficient to define the recombinant molecule by its principal biological activity, e.g. having protein A activity, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property." Colbert v. Lofdahl, 21 USPQ2d, 1068, 1071 (BPAI 1992).

Finally, a "CCR4 antagonist" also encompasses in its breadth antisense nucleic acids. The use of antisense nucleic acids in *in vivo* methods was well known in the art to be highly unpredictable, even though the level of skill in the art was high. Although antisense therapy has progressed in recent years, there is still a high level of unpredictability in the art. This unpredictability was summarized recently by Branch (TIBS 1998; 23:45-50). In particular, difficulties in ensuring that the oligo interacts with its single gene target versus other genes, and a variety of unexpected non-antisense effects, complicate the use of antisense compounds (e.g., summarized in Abstract). Thus in the absence of working examples or detailed guidance in the specification, the intended uses of any pharmaceutical composition comprising an antisense nucleic acid are fraught with uncertainties.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. For the reasons set forth *supra* it appears that undue experimentation would be required of one skilled in the art to practice the claimed invention using the guidance provided in the instant specification.

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Claim Rejections – 35 U.S.C. §§ 102 and 103

13. The following rejections under 35 U.S.C. §§ 102 are set forth with respect to linking claim 23 and dependent claims.

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

15. Claims 23-25, 27-30 and 35 are rejected under 35 U.S.C. 102(b) as being anticipated by Barrett et al. (U.S. Pat. No. 5,643,873, see entire document), as evidenced by Biedermann et al. (Eur. J. Immunol. 2002; 32 :3171-3180) and the specification on pages 7-8 disclosing that migration of CLA-expressing memory T cells into skin is a biological function of CCR4.

Barrett et al. teach the and claim methods of treating diseases associated with the presence of ELAM-1 by administering peptide inhibitors of ELAM-1 to reduce inflammation (see entire document, including claims and as summarized at columns 4-8). Barrett et al. teach that ELAM-1 was also known in the art as E-selectin (see e.g., column 2 at lines 40-55).

Barrett et al. also review that other inhibitors of E-selectin for reducing inflammation were known in the art, including sialyl Lewis^x and monoclonal antibodies to E-selectin (see e.g., columns 2-4, especially column 2 at lines 14-18 and 55-59).

Barrett et al. further review that inflammatory conditions mediated by selectins include forms of dermal inflammation, including atopic dermatitis (e.g., column 2, especially lines 18-24). Barrett et al. teach that the peptides and peptidomimetics of the invention can also be administered to treat E-selectin mediated conditions including atopic dermatitis (see column 23, especially lines 29-56).

Barrett et al. also review that E-selectin is expressed on endothelial cells, particularly after activation in the presence of inflammatory cytokines (see e.g., column 2, especially lines 40-55). Barrett et al. review that blocking of E-selectin inhibits adhesion of leukocytes to the endothelium and inhibits chemotaxis of the cells into the site of inflammation (i.e., inhibits extravasation through the endothelial barrier in response to soluble mediators present in the site of inflammation (chemotaxis), see columns 2-4).

Barrett et al. do not appreciate that administration of an inhibitor of E-selectin to a patient with atopic dermatitis would inherently function to inhibit the trafficking of systemic memory T cells to a site of inflammation wherein the site of inflammation is a site of atopic dermatitis. Neither do Barrett et al. appreciate that inhibitors of E-selectin inherently are "CCR4 antagonists".

However, inhibition of the trafficking of systemic memory T cells to a site of inflammation wherein the site of inflammation is a site of atopic dermatitis is inherent in a method that comprises administering inhibitors of E-selectin for the treatment of atopic dermatitis.

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Further, although inhibitors of E-selectin do not directly bind CCR4 or a ligand of CCR4, inhibitors of E-selectin are inherently CCR4 antagonists because they block a biological activity of CCR4 - the trafficking of memory T cells into a site of inflammation.

Biedermann et al. evidence that administration of an anti-E-selectin antibody or a sialyl Lewis^x analog each prevents migration of Th2 memory T cells into human skin (see e.g., Abstract).

In addition, the specification on pages 7-8 discloses that migration of CLA-expressing memory T cells into skin is a biological function of CCR4.

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the administration of peptide inhibitors of E-selectin, an anti-E-selectin antibody or a sialyl Lewis^x analog to a patient with atopic dermatitis.

When a claim recites using an old composition or structure (e.g. peptide inhibitors of E-selectin, anti-E-selectin-specific antibodies or a sialyl Lewis^x analog) and the use is directed to a result or property of that composition or structure (inhibition of trafficking of systemic memory T cells into a site of inflammation that is site of atopic dermatitis), then the claim is anticipated. See MPEP 2112.02. Also, see Bristol-Myers Squibb Co. v. Ben Venue Laboratories, Inc. 58 USPQ2d 1508 (CA FC 2001); Ex parte Novitski 26 USPQ 1389 (BPAI 1993); Mehl/Biophile International Corp. V. Milgraum, 52 USPQ2d 1303 (Fed. Cir. 1999); Atlas Powder Co. V. IRECO, 51 USPQ2d 1943 (Fed. Cir. 1999).

The reference teachings thus anticipate the instant claimed invention.

16. Claims 23-25, 28-31 and 35 are rejected under 35 U.S.C. 102(e) as being anticipated by Li et al. (US 2002/0098545, see entire document), as evidenced by the instant disclosure of the amino acid sequence of MDC in SEQ ID NO:6 and that MDC is a ligand of CCR4 on page 3 at lines 3-12.

Li et al. teach the chemokine CK β -13 (see entire document). Li et al. teach the amino acid sequence of CK β -13 in SEQ ID NO:2, as shown in Figure 1.

The amino acid sequence shown in Figure 1 of Li et al. is that of the chemokine MDC, as evidenced by SEQ ID NO:6 of the instant disclosure.

Li et al. also teach that antagonists of CK β -13 may be employed to treat atopic dermatitis (see page 16, especially paragraph 177).

Li et al. teach that antagonists of CK β -13 include monoclonal antibodies to CK β -13 (see paragraphs 116-123 and 171), and that the antibodies should be humanized for in vivo use (see especially paragraph 123).

Li et al. teach that antagonists of CK β -13 inhibit chemotaxis of cells, including T cells (e.g., paragraphs 174-177).

Li et al. do not appreciate that administration of an antibody antagonist of CK β -13 to a patient with atopic dermatitis would inherently function to inhibit the trafficking of systemic memory T cells to a site of inflammation wherein the site of inflammation is a site of atopic dermatitis. Neither do Li et al. appreciate that an antibody antagonist of CK β -13 is a "CCR4 antagonist".

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However, inhibition of the trafficking of systemic memory T cells to a site of inflammation wherein the site of inflammation is a site of atopic dermatitis is inherent in a method that comprises administering an antibody antagonist of CK β -13 for the treatment of atopic dermatitis. In addition, activated endothelial cells are inherently a site of inflammation in atopic dermatitis.

Further, MDC/CK β -13 is a ligand of CCR4; therefore an antibody to CK β -13 is a "CCR4 antagonist".

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent in a method comprising administering an antibody antagonist of CK β -13 for the treatment of atopic dermatitis.

When a claim recites using an old composition or structure (e.g. MDC/CK β -13-specific antibodies) and the use is directed to a result or property of that composition or structure (inhibition of trafficking of systemic memory T cells into a site of inflammation that is site of atopic dermatitis), then the claim is anticipated. See MPEP 2112.02. Also, see Bristol-Myers Squibb Co. v. Ben Venue Laboratories, Inc. 58 USPQ2d 1508 (CA FC 2001); Ex parte Novitski 26 USPQ 1389 (BPAI 1993); Mehl/Biophile International Corp. V. Milgraum, 52 USPQ2d 1303 (Fed. Cir. 1999); Atlas Powder Co. V. IRECO, 51 USPQ2d 1943 (Fed. Cir. 1999).

The reference teachings thus anticipate the instant claimed invention.

17. Claims 23-25, 28 and 35 are rejected under 35 U.S.C. 102(e) as being anticipated by Wells et al. (U.S. Pat. No. 6,150,132).

Wells et al. teach the cloning of K5.5 and its initial characterization as a chemokine receptor (see entire document, especially comment in column 7 at lines 15-23 regarding the nomenclature of the K5.5 molecule as CC-CKR-4). K5.5 is the same molecule as CCR4 (see also the amino acid sequence shown in Figure 3 and SEQ ID NO:20).

Wells et al. also teach that the K5.5(CCR4) receptor could be used to screen for agents useful in treating allergies, including atopic dermatitis (see columns 1-2, especially column 1 at line 60 to column 2 at line 25).

Wells et al. teach that MCP-1, MIP-1a and RANTES are chemokines that bind to the K5.5(CCR4) receptor and are capable of causing histamine release from basophils, and that an agent that is an antagonist (i.e., a "CCR4 antagonist") may be identified by the ability of the agent to block the release of histamine from basophils (bridging paragraph of columns 1-2). Wells et al. also teach assays for detecting binding of an agent to the K5.5(CCR4) receptor (column 2, especially lines 10-33).

Thus Wells et al. provide methods for identifying a CCR4 antagonists, i.e., an agent that blocks a testable function of K5.5(CCR4); and teach that such agents are useful in treating atopic dermatitis.

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Wells et al. do not appreciate that a method of treating atopic dermatitis by administering an agent that blocks a function of the K5.5 (CCR4) receptor would inherently function to inhibit the trafficking (i.e., chemotaxis) of systemic memory T cells to a site of inflammation wherein the site of inflammation is a site of atopic dermatitis.

However, inhibition of the trafficking of systemic memory T cells to a site of inflammation wherein the site of inflammation is a site of atopic dermatitis is inherent in a method that comprises administering an agent that blocks a function of K5.5(CCR4) for the treatment of atopic dermatitis. In addition, activated endothelial cells are inherently a site of inflammation in atopic dermatitis.

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent in a method comprising administering an agent that blocks a function of K5.5(CCR4) for the treatment of atopic dermatitis.

When a claim recites using an old composition or structure (e.g. a agent that blocks a function of K5.5(CCR4)) and the use is directed to a result or property of that composition or structure (inhibition of trafficking of systemic memory T cells into a site of inflammation that is site of atopic dermatitis), then the claim is anticipated. See MPEP 2112.02. Also, see Bristol-Myers Squibb Co. v. Ben Venue Laboratories, Inc. 58 USPQ2d 1508 (CA FC 2001); Ex parte Novitski 26 USPQ 1389 (BPAI 1993); Mehl/Biophile International Corp. V. Milgraum, 52 USPQ2d 1303 (Fed. Cir. 1999); Atlas Powder Co. V. IRECO, 51 USPQ2d 1943 (Fed. Cir. 1999).

The reference teachings thus anticipate the instant claimed invention.

18. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

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19. Claims 23-30, 32 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wells et al. (U.S. Pat. No. 6,150,132) in view of Heath et al. (J. Clin. Invest. 1997; 99:178-184).

The claims are drawn in view of the elected embodiments to a method of inhibiting trafficking of systemic memory T cells to a site of inflammation, wherein the site of inflammation is a site of atopic dermatitis, by administering a CCR4 antagonist that is an antibody to CCR4.

Wells et al. teach the cloning of K5.5 and its initial characterization as a chemokine receptor (see entire document, especially comment in column 7 at lines 15-23 regarding the nomenclature of the K5.5 molecule as CC-CKR-4). K5.5 is the same molecule as CCR4 (see also the amino acid sequence shown in Figure 3 and SEQ ID NO:20).

Wells et al. also teach that the K5.5(CCR4) receptor could be used to screen for agents useful in treating allergies, including atopic dermatitis (see columns 1-2, especially column 1 at line 60 to column 2 at line 25).

Wells et al. teach that MCP-1, MIP-1 α and RANTES are chemokines that bind to the K5.5(CCR4) receptor and are capable of causing histamine release from basophils, and that an agent that is an antagonist (i.e., a "CCR4 antagonist") may be identified by the ability of the agent to block the release of histamine from basophils (bridging paragraph of columns 1-2). Wells et al. also teach assays for detecting binding of an agent to the K5.5(CCR4) receptor (column 2, especially lines 10-33).

Thus Wells et al. provide methods for identifying a CCR4 antagonists, i.e., an agent that blocks a testable function of K5.5(CCR4); and teach that such agents are useful in treating atopic dermatitis.

Wells et al. also teach the production of antibodies to K5.5(CCR4), including monoclonal antibodies (see columns 4-5, especially column 4 at lines 47-56).

Wells et al. do not explicitly teach that monoclonal antibodies could be used as agents which bind K5.5(CCR4) and block a function of the K5.5(CCR4) receptor.

However, the production and application of antibodies as antagonists of chemokine receptor function was well known in the art at the time the invention was made.

For example, Heath et al. teach methods of producing antagonist monoclonal antibodies to chemokine receptors that neutralize the chemotaxis (cell migration/recruitment) induced in the cell type expressing the chemokine receptor associated with binding of a chemokine to that chemokine receptor (see entire document, but especially "Materials and Methods"). Heath et al. teach that antagonist monoclonal antibodies to chemokine receptors are therapeutically more beneficial than antibodies which block individual chemokines from binding to the chemokine receptor because more than one chemokine binds most chemokine receptors (e.g., "Discussion" on page 183, 1st full paragraph). Heath et al. also teach that antagonists of chemokine receptors are effective inhibitors of the recruitment of cells expressing that particular chemokine receptor, since the interaction of chemokines with the particular chemokine receptors expressed on different cell types are fundamental for the recruitment of that cell type (e.g. "Discussion", especially page 183, 1st partial paragraph).

Thus Heath et al. teach that antagonist monoclonal antibodies of chemokine receptors are desirable as therapeutic reagents to block recruitment of a cell type expressing that particular chemokine receptor when recruitment of that cell type contributes to an unwanted inflammatory response. Heath et al. also teach how to produce antagonist monoclonal antibodies to any chemokine receptor of interest by using transfectants expressing the chemokine receptor as an immunogen and screening tool.

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It would therefore have been obvious to the ordinary artisan at the time the invention was made to make monoclonal antibody antagonists of K5.5(CCR4) for use in a method of treating atopic dermatitis. The ordinary artisan at the time the invention was made would have been motivated to make monoclonal antibody antagonists of K5.5(CCR4) for use in treating atopic dermatitis as taught by Wells et al. because monoclonal antibodies were a well established agent for which in vivo applications were well characterized and the production of which was routine, as exemplified by the teachings of Heath et al.

In view of the teachings of Wells et al. of several assays by which antagonists of a K5.5(CCR4) function could be identified and the well known methods of producing antagonist monoclonal antibodies to chemokine receptors, as taught by Heath et al.; the ordinary artisan would have had a reasonable expectation that antagonist monoclonal antibodies to K5.5(CCR4) could be produced.

Although the combined teachings of the references were silent regarding the effect of administering a monoclonal antibody to K5.5(CCR4) for the treatment of atopic dermatitis with respect to the inhibitory effect on the trafficking of systemic memory T cells and the involvement of activated endothelial cells in atopic dermatitis; a monoclonal antibody that was selected for its ability to bind K5.5(CCR4) and to inhibit histamine release from basophils for use in treating atopic dermatitis would upon administration in vivo to a patient with atopic dermatitis necessarily mediate the inhibition of trafficking (i.e., chemotaxis) of systemic memory T cells to a site of inflammation that was an activated endothelial cell, would necessarily inhibit the cellular adhesion required for cellular trafficking, and would necessarily inhibit the binding of the chemokine TARC to CCR4.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

20. Claim 31 is rejected under 35 U.S.C. 103(a) as being unpatentable over Wells et al. (U.S. Pat. No. 6,150,132) in view of Heath et al. (J. Clin. Invest. 1997; 99:178-184) as applied to claims 23-30, 32 and 35 above, and further in view of Bendig (Methods: A Companion to Meth. Enzymol. 1995; 8:83-93).

The claims are drawn in view of the elected embodiments to a method of inhibiting trafficking of systemic memory T cells to a site of inflammation, wherein the site of inflammation is a site of atopic dermatitis, by administering a CCR4 antagonist that is a humanized antibody to CCR4.

Wells et al. in view of Heath et al. have been discussed supra.

Wells et al. in view of Heath et al. do not teach a method in which the antibody is humanized.

However, Bendig teaches the generation of humanized antibodies to antigens of interest (see entire document). A humanized antibody comprises a light chain and a heavy chain of a human antibody in which the complementarity determining regions (CDR) of a mouse monoclonal antibody to an antigen of interest has been substituted. Bendig teaches that humanized (with murine CDR regions) and chimeric (entire murine antigen binding domain) antibodies are less immunogenic, have a longer half life, and have more effective effector functions than rodent monoclonal antibodies when they are used in humans (see page 83, column 2 in particular).

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It would have been obvious to the ordinary artisan at the time the invention was made that any antibody for in vivo administration should be humanized. The ordinary artisan would have been motivated to humanize the antibody to avoid the art-recognized formation of human anti-rodent antibodies that would inactivate the administered anti-K5.5(CCR4) antibody in the absence of humanization. Methods of making humanized antibodies were well known in the art at the time the invention was made, as taught by Bendig; therefore the ordinary artisan at the time the invention was made would have had a reasonable expectation of producing a humanized antibody to K5.5(CCR4) and using it in the methods taught by Wells et al. in view of Heath et al. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Double Patenting

21. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

22. Claims 23-32 and 35 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-15 of U.S. Patent No. 6,245,332. Although the conflicting claims are not identical, they are not patentably distinct from each other.

The instant claims are drawn to a method of inhibiting trafficking of systemic memory T cells to a site of inflammation by administering an antagonist of CCR4, including wherein the site of inflammation is a site of atopic dermatitis and the CCR4 antagonist is an antibody to CCR4.

U.S. Patent No. 6,245,332 claims methods comprising administering a "CCR4 modulating agent" to modulate the trafficking of T cell populations that are in view of their cell surface phenotype "systemic memory T cells", and to treat "inflammatory skin disease" by administering a "CCR4 modulating agent" (e.g., independent claims 1 and 10-12). Dependent claims 8-9 and 13-14 further limit the "CCR4 modulating agent" to an antibody antagonist of CCR4, and claim 9 requires that the antibody be a monoclonal antibody.

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U.S. Patent No. 6,245,332 does not claim a method wherein the site of inflammation is a site of atopic dermatitis, nor does U.S. Patent No. 6,245,332 recite limitations regarding the cell type, the effects of the antagonist, or that the CCR4 antagonist antibody is humanized.

However, an "inflammatory skin disease" as recited in independent claim 12 of U.S. Patent No. 6,245,332 is disclosed in U.S. Patent No. 6,245,332 to include atopic dermatitis (e.g., column 5 at lines 21-24); thus the portion of the specification which provides support as to the invention claimed in U.S. Patent No. 6,245,332 indicates that atopic dermatitis is an obvious variation of the claimed invention.

It would therefore have been obvious to the ordinary artisan at the time the invention was made that the methods as claimed in U.S. Patent No. 6,245,332 could be applied to a site of inflammation of atopic dermatitis.

U.S. Patent No. 6,245,332 also does not explicitly recite the effect of administering a monoclonal antibody to CCR4 with respect to the inhibitory effect on the trafficking of systemic memory T cells to a site of inflammation that was an activated endothelial, on cellular adhesion required for cellular trafficking or on the binding of the chemokine TARC to CCR4. However, these effect are necessary outcomes of a method comprising administering a CCR4 antagonist antibody to inhibit trafficking of T cells as recited in U.S. Patent No. 6,245,332.

Further, it would have been obvious to the ordinary artisan at the time the invention was made that any antibody for in vivo administration should be humanized. The ordinary artisan would have been motivated to humanize the antibody to avoid the art-recognized formation of human anti-rodent antibodies that would inactivate the administered anti-CCR4 antibody in the absence of humanization. Methods of making humanized antibodies were well known in the art at the time the invention was made; therefore the ordinary artisan at the time the invention was made would have had a reasonable expectation of producing a humanized antibody to CCR4 and using it in the instant methods.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

23. No claim is allowed.

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24. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jessica Roark, whose telephone number is (703) 605-1209. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

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